Basal Pulmonary Vascular Resistance and Nitric Oxide Responsiveness Late After Fontan-Type Operation

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Background—The pulsatile nature of pulmonary blood flow is important for shear stress–mediated release of endothelium-derived nitric oxide (NO) and lowering pulmonary vascular resistance (PVR) by passive recruitment of capillaries. Normal pulsatile flow is lost or markedly attenuated after Fontan-type operations, but to date, there are no data on basal pulmonary vascular resistance and its responsiveness to exogenous NO at late follow-up in these patients.

Methods and Results—We measured indexed PVR (PVRI) using Fick principle to calculate pulmonary blood flow, with respiratory mass spectrometry to measure oxygen consumption, in 15 patients (median age, 12 years; range, 7 to 17 years; 12 male, 3 female) at a median of 9 years after a Fontan-type operation (6 atriopulmonary connections, 7 lateral tunnels, 2 extracardiac conduits). The basal PVRI was 2.11 ± 0.79 Wood unit (WU) times m² (mean ± SD) and showed a significant reduction to 1.61 ± 0.48 (P = 0.016) after 20 ppm of NO for 10 minutes. The patients with nonpulsatile group in the pulmonary circulation dropped the PVRI from 2.18 ± 0.34 to 1.82 ± 0.55 (P < 0.05) after NO inhalation.

Conclusions—PVR falls with exogenous NO late after Fontan-type operation. These data suggest pulmonary endothelial dysfunction, related in some part to lack of pulsatility in the pulmonary circulation because of altered flow characteristics. Therapeutic strategies to enhance pulmonary endothelial NO release may have a role in these patients. (Circulation. 2003;107:3204-3208.)

Key Words: Fontan procedure • pulmonary vascular resistance • endothelial dysfunction

The Fontan circulation is unique in exposing the pulmonary vascular bed to flow without a hydraulic pump as the driving force. In the absence of driving force from a ventricle, a low pulmonary vascular resistance is essential for the optimum functioning of the Fontan circulation. The Fontan operation leads to loss or severe attenuation of pulsatile pulmonary blood flow. Pulsatile flow is important for shear stress–mediated release of endothelium-derived nitric oxide (NO) and lowering of pulmonary vascular resistance by passive recruitment of capillaries. Even though exogenous NO has been used therapeutically to reduce pulmonary vascular resistance and improve cardiac output in early postoperative states after Fontan operation, to our knowledge, there are no data on the basal pulmonary vascular resistance and its responsiveness to NO late after Fontan operation.

In this study, we measured the basal pulmonary vascular resistance (PVR) and its responsiveness to exogenous NO in patients with Fontan operation late after repair to investigate the integrity of pulmonary vascular endothelium in these patients.

Methods

Study Population

We studied 15 patients with Fontan circulation to assess basal pulmonary vascular resistance and its response to inhaled NO during cardiac catheterization under general anesthesia. The study protocol received approval of the ethics committee of Great Ormond Street Hospital and Institute of Child Health. Informed consent was obtained from all participating patients and parents. The study protocol was carried out at the end of cardiac catheterization performed as a routine diagnostic study or for specific purposes such as occlusion of fenestration or collaterals.

Cardiac catheterization and angiography were performed under general anesthesia with muscle paralysis in inspired oxygen concentration less than 0.3, which then remained constant throughout the study. All patients were intubated with a cuffed endotracheal tube and ventilated with a Servo 900B ventilator, and the exhaled gas was collected in a mixing chamber and analyzed using a mass spectrometer (Amis 2000, Innovision) to measure oxygen consumption. A transesophageal echocardiogram was performed. Routine diagnostic cardiac catheterization and angiography was performed to obtain basic hemodynamic data and rule out any shunt, obstruction, or significant atriocentric or semilunar valve regurgitation. All pressure measurements were done with cessation of ventilation.

Study Protocol

After routine hemodynamic and angiographic assessment and in the absence of significant shunts or branch pulmonary artery stenosis, we measured the oxygen consumption (VO₂) and calculated pulmonary blood flow by using the Fick principle with arteriovenous oxygen difference obtained from a constant site in a branch pulmonary artery and left atrium or left ventricle in absence of right to left shunt. After baseline measurements, 20 ppm NO was administered

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through the ventilator circuit with continuous analysis of the dose delivered and monitoring of NO2 levels. After 10 minutes of NO, VO2 was measured and pulmonary blood flow was calculated again. These measurements were repeated after a washout period of 10 minutes.

The pulmonary vascular resistance was calculated as follows:

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PVR = \frac{(\text{mPAP} - \text{mPCWP})/Qp}{Qp} \]

where mPAP indicates mean pulmonary artery pressure, mPCWP indicates mean pulmonary capillary wedge pressure, which was taken as a measure of mean left atrial pressure, and Qp indicates pulmonary blood flow.

Pressure measurements were done in apnea and after blood sampling to avoid fluctuations in VO2 and blood gases. The PVR index (PVRI, WU−m2) was calculated by using cardiac index (Qp/body surface area) in the denominator.

Data are described as median and range for continuous variables and mean and standard deviations for discrete variables. We studied the relationship of age, NYHA functional class, and duration after Fontan operation to the baseline PVRI and assessed the effect of NO on PVRI of the group as a whole, on the subgroup with PVRI >WU·m2, and on groups with different palliations before their Fontan operation and different pulmonary artery flow patterns after their Fontan operations. Statistical analysis was done by 2-tailed, paired t tests for parameters before and after intervention with exogenous NO and 2-tailed unpaired t tests when comparing 2 groups. Statistical significance was defined as P<0.05.

**Results**

The demographic and clinical information of the study group is described in the Table. The median age of the patients was 12 years (range, 7 to 17 years), and the median duration after operation was 9 years (range, 0.08 to 15 years). The diagnosis was tricuspid atresia in 5, with concordant ventriculoarterial connections in 3 and discordant in 2, double-inlet left ventricle in 6, pulmonary atresia with intact ventricular septum in 3, and atrioventricular and ventriculoarterial discordance in 1. The Fontan operation involved atroipulmonary connection in 6, lateral tunnel in 7, and extracardiac conduits in 2. Three patients were in NYHA class 3, 2 were in class 2, and the rest were in class 1.

The mean cardiac index and mean pulmonary vascular resistance index was 2.48±0.57 L/min per m2 and 2.11±0.79 WU·m2, respectively, in the study group.

Thus, the mean pulmonary vascular resistance index was elevated in our study group (normal values <2 WU·m2). To our knowledge, this is the first documentation of elevated PVRI late after Fontan operation. The age of the patients and duration of follow-up after the operation had no correlation with PVRI (Figures 1 and 2, respectively). When the patients were divided into 2 groups on the basis of NYHA functional class, group A (NYHA 1) had a significantly lower mean PVRI (1.72±0.38 WU·m2) compared with group B (NYHA 2 and 3) (2.82±0.88) (P<0.05) (Figure 3).

After 20 ppm of inhaled NO for a period of 10 minutes, the mean cardiac index dropped marginally from 2.48±0.57 to 2.38±0.83 L/min per m2 (P=0.489); however, the mean PVRI dropped from 2.11±0.79 to 1.61±0.48 WU·m2 (P=0.016, paired t test) (Figure 4). The NO inhalation produced no significant change in the mean left ventricular
end-diastolic pressure (7.8±2.6 to 7.4±3.1 mm Hg, P=0.32) and the V̇O₂ (3.6±0.8 to 3.5±0.8 mL/kg per min, P=0.37).

Interestingly, of the patients in the study group who had elevated PVRI (>2 WU·m⁻²), 6 of the 7 showed a dramatic response to exogenous NO (2.64±0.77 to 1.75±0.54, P<0.05, paired t test) compared those with PVRI <2, who showed no significant change (1.59±0.33 to 1.47±0.4, P=0.2) (Figure 5).

The basal PVRI did not show any important differences between patients who had a pulmonary band as an initial palliation (n=5) compared with those who had systemic to pulmonary artery shunts (n=9). The response to NO was, however, more significant in those with a band (2±0.22 to 1.47±0.22, P=0.006, paired t test) (Figure 6).

We found different pressure tracings in pulmonary arteries of patients with atriopulmonary and some lateral tunnel connections and extracardiac conduits. On the basis of pulse pressures (difference between peak and nadir), we divided patients into groups with pulsatile flow (mainly seen with atriopulmonary [6] and 1 lateral tunnel connection; n=7) and nonpulsatile flow (2 extracardiac conduits, 6 lateral tunnels). The mean pulse pressure in pulsatile group was 3.7 and in the nonpulsatile group 0.3.

There was no significant difference between the basal PVRI in the 2 groups; however, the nonpulsatile group dropped the PVRI from 2.18±0.34 to 1.82±0.55, P<0.05 (Figure 7). This may indicate that the pulmonary endothelial dysfunction is related, at least in some part, to lack of pulsatility in the pulmonary circulation because of altered flow characteristics after Fontan operation.

Discussion

The Fontan operation has evolved over the last 3 decades, with many changes in the selection criteria and preoperative preparation leading to a significant reduction in early mortality and morbidity.1,2 Although the long-term outlook for contemporary series remains uncertain, historical cohorts report severe functional decline, congestive heart failure, and late death with increasing follow-up.1,9-11 The reasons for deterioration are multifactorial, but a low pulmonary vascular resistance remains an important prognostic factor for a good functional result after the Fontan operation.12

NO has been used to treat pulmonary endothelial dysfunction resulting from cardiopulmonary bypass after Fontan operation.5,13 However, to our knowledge, there are no studies examining the effect of inhaled NO on pulmonary vascular resistance late after Fontan-type operations.

NO plays an important role in regulation of basal pulmonary vascular tone.14-16 Supplemental inhaled NO has no effect on basal pulmonary vascular tone or pulmonary blood flow,17 but blockade of NO production leads to pulmonary vasoconstriction and reduced pulmonary blood flow in the normal lung.18-20

In our study, the mean PVRI was elevated in patients late after Fontan-type operation. There was no correlation between the age at follow-up and duration after surgery and elevated PVRI. This probably suggests that the elevated PVRI is not a consequence of the Fontan state in patients deemed as “good Fontans” but may reflect the preparation during their initial staging operations.

Supplemental inhaled NO led to a fall in PVR, suggesting that basal PVR is increased, presumably as a result of endothelial dysfunction. There are many possible reasons for

Figure 3. NYHA class and PVRI. Patients with higher PVRI were in NYHA classes 2 and 3. *P<0.05.

Figure 4. Effect of exogenous NO on PVRI late after Fontan operation. NO caused a significant drop of mean PVRI in the study group (*P=0.016).

Figure 5. Effect of exogenous NO on patients with PVRI >2 (*P=0.023).

Figure 6. Effect of NO on PVRI of patients with pulmonary artery band as initial palliation showed a significant response (*P=0.006) compared with the shunt group (P=0.04).
pulmonary endothelial dysfunction after Fontan operation. The Fontan circulation leads to alterations in the flow patterns in the pulmonary vascular bed. There is a phasic dependence of pulmonary blood flow with changes in intrathoracic pressure but a loss or severe attenuation of cardiac pulsatility in the pulmonary vascular bed. The pulsatile flow is important for maintaining a low resistance in the pulmonary vasculature by the passive recruitment of capillaries and shear stress–mediated release of NO causing endothelial relaxation. Indeed, pulsatile flow has been shown to be a more potent stimulus for release of NO to the same volume of laminar flow. Pulsatile shear stress acts on the endothelium via diverse mechanisms. Experimentally, induction of hyperpolarization of endothelial cell causes elevation of cGMP via an NO-dependent mechanism, redistribution of the endothelial cytoskeletal protein, actin, and upregulation of NO synthase gene transcription, which may be caused by pulsatile shear stress. Reduced pulsatile shear stress in the Fontan pulmonary circulation, thus, may downregulate the endothelial NO synthase expression and attenuate endothelial-dependent vasodilatation.

On this basis, the degree of elevation of PVR or NO responsiveness might be expected to correlate with the residual pulsatility in the pulmonary circulation in our patients. Although some pulsatility was preserved in those with atriopulmonary connection and lateral tunnel Fontan with dilated right atrium, pulsatility was essentially absent in those with an extracardiac conduit. Although there was no difference in the basal PVRI between the 2 groups, we found that the nonpulsatile group responded to exogenous NO with a significant drop in their PVRI compared with those with pulsatile flow. This may reflect the altered pulmonary endothelial function attributable to important changes in flow characteristics after some types of Fontan operations. However, it is difficult to rule out the impact of pre-Fontan hemodynamics and flow patterns in the pulmonary circulation of this cohort of patients and attribute these changes solely to pulsatility or the lack of it.

Recent data are somewhat counterintuitive with regards to the magnitude of shear stress and type of Fontan circulation. Using 3D phase-contrast MRI, increasing shear stress was detected at the anastomosis in Fontan circuits with total cavopulmonary connection compared with atriopulmonary connections. This is attributable to circular swirling vortices in the laminar flow and increase in circumferential stress. However, this study did not attempt to measure shear stress in the more peripheral pulmonary arteriolar bed, the major resistance vessels responsible for modulation of PVR.

Therefore, the issues surrounding pulmonary endothelial dysfunction in Fontan circulation are complex and remain fully to be explored. Furthermore, we cannot exclude an entirely separate mechanism for the effect of NO in our patients. Inhaled NO is a potent pulmonary vasodilator in the presence of alveolar hypercapnia, hypoxia, pulmonary parenchymal disease, and circulating vasoconstrictors such as endothelins. Although we can exclude ventilatory and parenchymal abnormalities, the role of spontaneous respiration and gravity on pulmonary blood flow could not be assessed in our patients. Also, inhaled NO may be effecting pulmonary vasodilatation by antagonizing a constrictor. No matter what the mechanism, our findings suggest that some patients may benefit from treatment to enhance or replace pulmonary NO production or release. There are no specific data regarding such agents, but it is known that angiotensin-converting enzyme inhibitors (known to increase NO effects and decrease oxidants) fail to improve functional capacity in unslecteded patients after Fontan operations.

Limitations
This cohort study investigates a small nonselective group of patients after Fontan operation; hence, interpretation of comparison between smaller subgroups should be cautious. Also, all patients were studied under general anesthesia; therefore, the effect of spontaneous respiration and gravity could not be taken into account. However, any influence of ventilation problems on PVR could safely be excluded.

In summary, pulmonary vascular resistance is elevated and falls in response to exogenous NO, late after Fontan operation. There is no difference in the basal PVR and its response to exogenous NO between different Fontan-type operations. Elevated PVR correlates with poor functional performance late after Fontan operations. Pharmacological manipulation of pulmonary vascular tone may have a therapeutic role in selected patients late after Fontan-type operations.

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